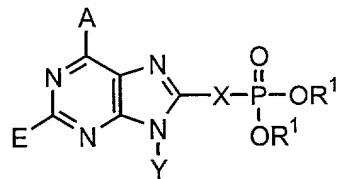


We claim:

1. A compound of formula 1:



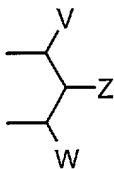
A is selected from the group consisting of -NR⁸₂, NHSO₂R³, -OR⁵, -SR⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-OR³, -CONHR³, -NR²₂, and -OR³, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, alkylaryl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-alkylhydroxy, or together R¹ and R¹ are -alkyl-S-S-alkyl to form a cyclic group, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR², -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together they form a bidendate alkyl;

R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and pharmaceutically acceptable prodrugs and salts thereof.

2. The compounds of claim 1 with the proviso that R^1 is not lower alkyl of 1-4 carbon atoms.

3. The compounds of claim 1 wherein A is selected from the group consisting of -NR⁸₂, halogen, lower alkyl, lower perhaloalkyl, and lower alkoxy.

4. The compounds of claim 1 wherein E is -H, halogen, lower perhaloalkyl, -CN, lower alkyl, lower alkoxy, and lower alkylthio.

5. The compounds of claim 1 wherein X is selected from the group consisting of alkylamino, alkyl, alkynyl, alkoxyalkyl, alkylthio, aryl, 1,1-dihaloalkyl, carbonylalkyl, heteroaryl, alkylcarbonylamino, and alkylaminocarbonyl.

6. The compounds of claim 5 wherein X is alkyl substituted with 1 to 3 substituents selected from the group consisting of halogen, phosphonate, -CO₂H, -SO₃H, and -OH.

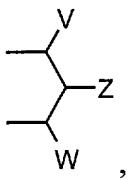
7. The compounds of claim 5 wherein X is selected from the group consisting of alkylaminocarbonyl, alkoxyalkyl, and heteroaryl.

8. The compounds of claim 7 wherein X is selected from the group consisting of methoxymethyl and optionally substituted furanyl.

9. The compounds of claim 1 wherein Y is selected from the group consisting of aralkyl, aryl, alicyclic, and alkyl.

10. The compounds of claim 1 wherein each R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted phenyl, optionally substituted benzyl, optionally substituted alkylaryl, -C(R²)₂OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂-OC(O)SR³, -alkyl-S-C(O)R³, alkyl-S-

S-alkylhydroxyl, and -alkyl-S-S-alkylhydroxy, or together R¹ and R¹ are alkyl-S-S-alkyl to form a cyclic group, or R¹ and R¹ together are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR², -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic.

11. The compounds of claim 10 wherein each R¹ is independently selected from the group consisting of optionally substituted phenyl, optionally substituted benzyl, -C(R²)₂OC(O)R³, -C(R²)₂OC(O)OR³, and -H.

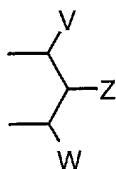
12. The compounds of claim 10 wherein R¹ is H.

13. The compounds of claim 10 wherein at least one R¹ is aryl, or -C(R²)₂-aryl.

14. The compounds of claim 10 wherein at least one R¹ is -C(R²)₂-OC(O)R³, -C(R²)₂-OC(O)OR³, -C(R²)₂-OC(O)SR³.

15. The compounds of claim 10 wherein at least one R¹ is alkyl-S-S-alkylhydroxyl, -alkyl-S-C(O)R³, and -alkyl-S-S-alkylhydroxy, or together R¹ and R¹ are alkyl-S-S-alkyl to form a cyclic group.

16. The compounds of claim 10 wherein together R¹ and R¹ are



to form a cyclic group;

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR², -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

17. The compounds of claim 16 wherein V and W both form a 6-membered carbocyclic ring substituted with 0-4 groups, selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, and alkoxy; and Z is R^2 .

18. The compounds of claim 16 wherein V and W are hydrogen; and Z is selected from the group consisting of hydroxyalkyl, acyloxyalkyl, alkyloxyalkyl, and alkoxycarboxyalkyl.

19. The compounds of claim 16 wherein V and W are independently selected from the group consisting of hydrogen, optionally substituted aryl, and optionally substituted heteroaryl, with the proviso that at least one of V and W is optionally substituted aryl or optionally substituted heteroaryl.

20. The compounds of claim 1 wherein together R^1 and R^1 are optionally substituted lactones attached at the omega position.

21. The compounds of claim 10 wherein R^1 is alicyclic where the cyclic moiety contains carbonate or thiocarbonate.

22. The compounds of claim 21 wherein together R^1 and R^1 are optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen.

23. The compounds of claim 1 wherein A is selected from the group consisting of - NR^8_2 , and halogen;

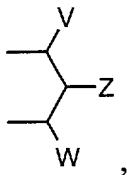
E is selected from the group consisting of -H, halogen, -CN, lower alkyl, lower perhaloalkyl, lower alkoxy, and lower alkylthio;

X is selected from the group consisting of alkylamino, alkyl, alkoxylalkyl, alkynyl, alkylthio, aryl, heteroaryl, alkylcarbonylamino, 1,1-dihaloalkyl, carbonylalkyl, alkyl(OH), alkyl(sulfonate), and alkylaminocarbonyl; and

R^4 and R^7 are selected from the group consisting of -H, and lower alkyl.

24. The compounds of claim 23 wherein
Y is selected from the group consisting of aralkyl, aryl, alicyclic, and alkyl.

25. The compound of claim 24 wherein R¹ and R¹ together are



V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or
together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R⁹ is selected from the group consisting of alkyl, aralkyl, and
alicyclic.

26. The compounds of claim 23 wherein A is -NR⁸₂;

E is selected from the group consisting of -H, -Cl, and -SCH₃; and X is selected from the group consisting of optionally substituted furanyl and alkoxyalkyl.

27. The compounds of claim 26 wherein A is -NH₂; E is selected from the group consisting of -H, -Cl, and -SCH₃;
 X is selected from the group consisting of 2,5-furanyl, and methoxymethyl; and
 Y is lower alkyl.

28. The compound of claim 27 wherein E is -H, X is 2,5-furanyl, and Y is neopentyl.

29. The compound of claim 28 wherein R¹ is -CH₂O-C(O)-C(CH₃)₃ or its HCl salt.

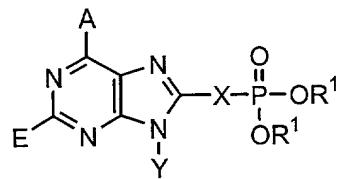
30. The compound of claim 27 wherein E is -SCH₃, X is 2,5-furanyl, and Y is isobutyl.

31. The compound of claim 30 wherein R¹ is -CH₂O-C(O)-C(CH₃)₃ or its HCl salt.

32. The compound of claim 27 wherein E is -H, X is 2,5-furanyl, and Y is 1-(3-chloro-2,2-dimethyl)-propyl.

33. The compound of claim 32 wherein R¹ is -CH₂O-C(O)-C(CH₃)₃ or its HCl salt.

34. A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula (1):



wherein

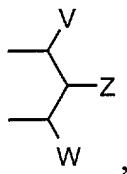
A is selected from the group consisting of -NR⁸₂, NHSO₂R³, -OR⁵, -SR⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-OR³, -CONHR³, -NR², and -OR³, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, alkylaryl, -C(R²)₂OC(O)NR², -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-alkylhydroxy, or together R¹ and R¹ are -alkyl-S-S-alkyl to form a cyclic group, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

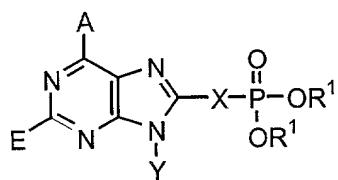
R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together they form a bidendate alkyl;

R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R¹⁰ is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;

R¹¹ is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and pharmaceutically acceptable prodrugs and salts thereof.

35. A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula (1):



wherein

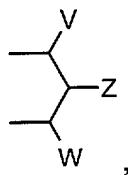
A is selected from the group consisting of -NR⁸₂, NHSO₂R³, -OR⁵, -SR⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-OR³, -CONHR³, -NR²₂, and -OR³, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, alkylaryl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R¹ and R¹ are -alkyl-S-S-alkyl to form a cyclic group, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy carboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together they form a bidendate alkyl;

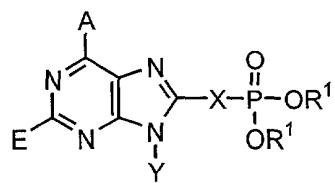
R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R¹⁰ is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;

R¹¹ is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and

pharmaceutically acceptable prodrugs and salts thereof.

36. A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula (1):



wherein

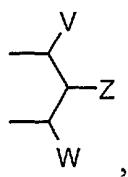
A is selected from the group consisting of -NR⁸₂, NHSO₂R³, -OR⁵, -SR⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)₂R³, -C(O)-OR³, -CONHR³, -NR²₂, and -OR³, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, alkylaryl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R¹ and R¹ are -alkyl-S-S-alkyl to form a cyclic group, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together they form a bidendate alkyl;

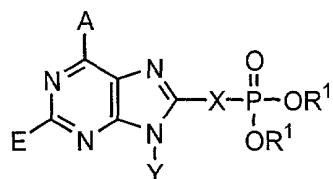
R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R¹⁰ is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and

pharmaceutically acceptable prodrugs and salts thereof.

37. A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula (1):



wherein

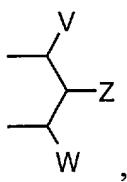
A is selected from the group consisting of -NR⁸₂, NHSO₂R³, -OR⁵, -SR⁵, halogen, lower alkyl, -CON(R⁴)₂, guanidine, amidine, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR²₂;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R³, -S(O)R³, -C(O)-OR³, -CONHR³, -NR²₂, and -OR³, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, alkylaryl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-alkylhydroxy, or together R¹ and R¹ are -alkyl-S-S-alkyl to form a cyclic group, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

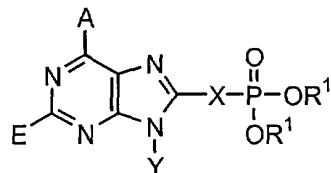
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-OH$, $-NH_2$ and $-OR^3$; and pharmaceutically acceptable prodrugs and salts thereof.

38. A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor which binds to the AMP site of FBPase.

39. The method of claim 38 wherein said inhibitor is compound of formula (1):



wherein

A is selected from the group consisting of $-NR_2^8$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

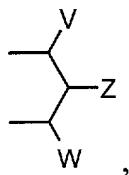
E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR_2^7$;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR_2^2$, and $-OR^3$,

all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, alkylaryl, -C(R²)₂OC(O)NR², -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R¹ and R¹ are -alkyl-S-S-alkyl to form a cyclic group, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N³, -CH₂NR², -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- a) V, Z, W are not all -H; and
- b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

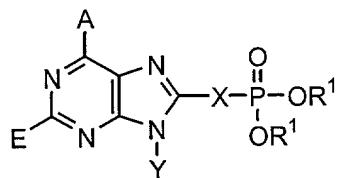
R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-OH$, $-NH_2$ and $-OR^3$; and pharmaceutically acceptable prodrugs and salts thereof.

40. The method of claim 39 wherein said disease is atherosclerosis.

41. A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor which binds to the AMP site of FBPase.

42. The method of claim 41 wherein said inhibitor is a compound of formula (1):



wherein

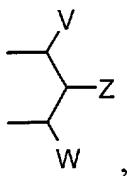
A is selected from the group consisting of $-NR_2^8$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or together with Y forms a cyclic group including cyclic alkyl, heterocyclic, and aryl;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-\text{C}(\text{O})\text{R}^3$, $-\text{S}(\text{O})_2\text{R}^3$, $-\text{C}(\text{O})-\text{OR}^3$, $-\text{CONHR}^3$, $-\text{NR}^2\text{C}(\text{O})-\text{R}^3$, and $-\text{OR}^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-\text{C}(\text{R}^2)_2\text{aryl}$, alkylaryl, $-\text{C}(\text{R}^2)_2\text{OC}(\text{O})\text{NR}^2$, $-\text{NR}^2\text{C}(\text{O})-\text{R}^3$, $-\text{C}(\text{R}^2)_2\text{OC}(\text{O})\text{R}^3$, $\text{C}(\text{R}^2)_2\text{O}-\text{C}(\text{O})\text{OR}^3$, $-\text{C}(\text{R}^2)_2\text{OC}(\text{O})\text{SR}^3$, alkyl-S-C(O)R³, alkyl-S-S-alkylhydroxy, and alkyl-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-\text{R}^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, or aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, and aryloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR², -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together they form a bidendate alkyl;

R⁹ is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R¹⁰ is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;

R¹¹ is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and

pharmaceutically acceptable prodrugs and salts thereof.

43. The method of claims 34, 35, 36, 37, 38, 39, 40, 41, or 42 wherein said compound is administered orally.